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Efficacy of lateral bone augmentation prior to implant placement: A systematic review and meta-analysis.

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Abstract

Aim: The aim of the current systematic review was to critically appraise evidence from randomized and prospective non-randomized comparative clinical trials about the efficacy of lateral bone augmentation prior to implant placement and their outcome regarding bone-width gain.

Material and Methods: Eight databases were searched until May 2018 for randomized and prospective non-randomized comparative trials on lateral bone augmentation prior to implant placement. After elimination of duplicate studies, data extraction and risk-of-bias assessment according to the Cochrane guidelines, random-effects meta-analyses of Mean Differences (MD) or Relative Risks (RR) and their 95% CIs were performed, followed by subgroup, meta-regression, and sensitivity analyses.

Results: A total of 25 trials (16 randomized / 9 non-randomized) were identified, which included a total of 553 patients (42.2% male; mean age of 43.9 years). In these included studies and populations, various modalities for primary lateral bone augmentation rendered implant placement feasible. Small discrepancies were found between overall clinical and radiographic gain (pooled gains of 3.45 ± 1.18 mm versus 2.90 ± 0.83 mm, respectively), but were not statistically significant. Bone width gain was significantly inversely associated with baseline bone width (pooled effect: -0.35 mm/mm; 95% CI: -0.63 to -0.07 mm; p=0.01). % graft resorption demonstrated a correlation with patient age (36% /year, 95% CI: -0.62 to -0.11 mm; p=0.01). The presence of xenograft added to autologous graft led to less resorption compared to autologous graft alone (MD: 1.06 mm; 95% CI: 0.21 to 1.92 mm; p=0.01). Barrier membrane did not yield significant difference in terms of bone width gain (MD: -0.33 mm; 95% CI: -2.24 to 1.58 mm; p>0.05) and graft resorption (MD: 0.84 mm; 95% CI: -1.42 to 3.09 mm; p>0.05).

Conclusions: Initially smaller bone dimension are associated with larger bone width gain, which indicates that a severe lateral bone deficiency can be effectively augmented applying primary lateral bone augmentation. Both patients' age and recipient site (maxilla or mandible) seem to influence graft resorption. The addition of a xenograft can be helpful in reducing graft resorption.

Clinical Relevance:

Scientific rationale for the study

Whether solely primary lateral bone augmentation leads to sufficient ridge width for subsequent implant placement, is still scarcely reported in detail.

Principal findings

Most of the studies (24 out of 25 included) reported that lateral bone augmentation allowed for subsequent implant placement. Nevertheless, only a small number of studies reported on the proportion of implants placed according to the planning/ the placement in a prosthetically ideal position, the need for a narrower implant diameter or the proportion of implants which needed additional bone augmentation procedures.

The ridge width gain is significantly influenced by the ridge width prior to augmentation. Furthermore, bone width gain and graft resorption are influenced by baseline ridge width, age and jaw. The presence of xenogeneic graft material seems favorable in terms of dimensional stability.

Practical implications

Primary lateral bone augmentation represents a predictable procedure in order to gain sufficient ridge width for placing implants.

K E Y W O R D S

systematic review, dental implant, implant placement, lateral bone augmentation, primary bone augmentation, ridge width

1 | INTRODUCTION

1.1 | Rationale

Implant placement at edentulous areas with severe bone deficiencies often represents a challenging situation for clinicians. In order to correct bone dimensions insufficient for implant placement, numerous bone augmentation procedures have been described in the literature (Esposito, et al., 2009; Jensen & Terheyden, 2009). Bone augmentation may be carried out prior to or simultaneous with implant placement. The choice whether or not primary bone augmentation is needed depends on a number of factors: the amount of bone lacking; the area within the dental arch; feasibility of implant placement in a proper position and with primary stability; the expected size of implant surface exposure at the time of implant placement. Available evidence demonstrates predictable correction of bone deficiencies using bone augmentation procedures (Benic & Hammerle, 2014). Moreover, implant survival rates are similar both for implants placed in pristine bone as well as for implants placed in augmented bone (Hammerle, Jung & Feloutzis, 2002).

The use of a variety of materials and techniques has been published (Aghaloo & Moy, 2007; Chiapasco & Casentini, 2018; Donos, Mardas & Chadha, 2008). The materials applied encompass autologous bone, allogenic bone, xenogenic bone and synthetic bone substitute materials. All of these biomaterials have been applied as blocks or in particulated form. Autologous bone grafts are predominantly harvested from intraoral sources such as the mandibular ramus, the chin region, the maxillary tuberosity, and the nasal spine (Chappuis, et al., 2018; Cordaro, Amade & Cordaro, 2002; Cordaro, Torsello, Morcavallo & di Torresanto, 2011; Meijndert, Raghoebar, Meijer & Vissink, 2008; Tolstunov, 2009). When larger amounts of autologous bone are needed, extraoral sites are chosen including the iliac crest and the external plate of the calvarium (Chiapasco, Autelitano, Rabbiosi & Zaniboni, 2013; Chiapasco, Di Martino, Anello, Zaniboni & Romeo, 2015). Moreover, autologous and allogenic bone have been combined with bone substitute materials (Wang, Misch & Neiva, 2004). The reason for combining these materials is to expand the volume of grafting material available and to reduce the resorption of the transplanted autologous or allogenic bone. A clinical benefit of using allogenic bone, xenogenic bone or synthetic bone substitute materials is to reduce or completely avoid the morbidity associated with bone harvesting procedures. Growth factors such as rhBMP2 and enhancers such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have been used alone or

in combination with the above-described materials (Badr, Coulthard, Alissa & Oliver, 2010; Barbu, et al., 2016; de Freitas, et al., 2013).

A variety of techniques, such as ridge-splitting, guided bone regeneration (GBR) procedures, transplantation of autologous bone and application of bone substitute materials have been introduced (Chiapasco, et al., 2015; Costa, Pelegrine, Fagundes, Simoes & Taha, 2011; Hammerle, et al., 2002; Scipioni, Bruschi & Calesini, 1994; Urban, Nagursky & Lozada, 2011). They have shown positive results for the correction of bone defects in the alveolar ridge. So far, no material and/or technique demonstrated to be superior in terms of feasibility of implant placement and bone gain.

Numerous publications investigated horizontal bone augmentation both prior to and simultaneous with implant placement (Sanz-Sanchez, Ortiz-Vigon, Sanz-Martin, Figuero & Sanz, 2015). Most of the systematic reviews available have concomitantly addressed staged and simultaneous bone augmentation (Aghaloo & Moy, 2007; Esposito, et al., 2009; Sanz-Sanchez, et al., 2015). Limited evidence exists regarding only primary horizontal bone augmentation. Furthermore, scarce information is available assessing different approaches – i.e. materials and/or techniques – with respect to their ability to successfully regenerate bony ridge defects prior to implant placement.

The primary aim of the reconstruction of deficient ridges is to improve the ridge profile in order to facilitate subsequent prosthetic rehabilitation. The prosthetic procedure predominantly applied after bone augmentation is an implant-borne reconstruction. Hence, the success of primary bone augmentation procedures may be assessed by the feasibility of implant placement following bone healing.

1.2 | Objectives

The aim of the current systematic review was to critically appraise evidence from randomized and prospective non-randomized comparative clinical trials on humans about the efficacy of primary lateral bone augmentation prior to implant placement and the primary outcome of bone-width gain.

2 | MATERIALS AND METHODS

2.1 | Protocol, registration, and eligibility criteria

The review protocol was developed a priori according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Liberati, et al., 2009) and registered in

PROSPERO (International prospective register of systematic reviews; CRD42018093073). The Participants-Intervention-Comparison-Outcome-Study design (PICOS) framework was established as follows: Participants – patients in need of primary lateral bone augmentation for increasing bone width in order to place dental implants at one or more sites in either jaw; Intervention – primary lateral bone augmentation using different materials/techniques; Comparison – any material/technique other than the Intervention group; Outcome (primary) – amount (width) of alveolar ridge gained through the augmentation procedure (measured radiographically or clinically), which was defined as bone width at re-entry for implant insertion minus pre-augmentation bone width; and Study design – randomized and prospective non-randomized comparative clinical trials. Additional secondary outcomes included: (i) feasibility of implant placement after an adequate healing time (with or without additional bone augmentation at the time of implant placement); (ii) amount of bone graft resorbed (defined as bone width at re-entry for implant insertion minus immediate post-augmentation bone width); (iii) % bone graft resorption from the added graft (defined as the amount of bone graft resorbed divided by the post-augmentation width addition); (iv) adverse events at recipient site (such as infection, graft failure, wound dehiscence) or at donor site (nerve damage, infection); (v) Patient-Reported Outcome Measures (PROMS) (morbidity: swelling, pain); (vi) implant failure (defined either as need for implant removal or as salvageable complication / peri-implant disease); and (v) marginal bone level changes after implant insertion/loading. Positive values for the primary outcome of bone width gain indicate that the bone width was increased compared to baseline. Negative values for the secondary outcome of bone graft resorption indicate that the bone graft added during the augmentation procedure had been resorbed at the re-entry surgery where implant placement was planned.

The focused question this systematic review answered was: “In patients presenting with insufficient alveolar ridge width for implant placement, does primary lateral bone augmentation lead to sufficient gain in bone width (to allow for subsequent implant placement)?"

Excluded were clearly retrospective studies or studies with unclear design, case reports or case series, animal studies, pre-clinical, and non-clinical studies. No limitations were set regarding publication year, publication language, or publication type.

2.2 | Information sources and search

Electronic searches were performed in the following eight electronic general, open access,

regional and grey literature bibliographic databases: MEDLINE (searched via PubMed), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts of Reviews of Effects (DARE), Embase, Scopus, Web of Knowledge, and Virtual Health Library (including Bibliografia Brasileira de Odontologia and LILACS). Aditionally, Directory of Open Access Journals, Digital Dissertations (searched via UMI Proquest), metaRegister of Controlled Trials, WHO trials search portal and Google Scholar were searched manually. No search filters were applied other than trials on humans and dentistry, where available. Hand searching was also performed from the reference/citation lists of eligible studies and relevant systematic reviews for additional studies (Appendix 1).

2.3 | Study selection

Study selection was performed in duplicate by two authors (NN, HCL) independently. Any disagreement in the process was solved by discussion with the other two authors (SNP, CHFH). First the titles and then the abstracts of all studies derived from the search were screened against the inclusion criteria. If title or abstract did not provide sufficient information regarding exclusion of a study, the decision was based on the study's full text.

2.4 | Data items and data collection process

Data extraction was made independently by two authors (NN, HCL) using pre-specified extraction tables covering study characteristics (design, setting, and country), patient characteristics (number, sex, age, systemic health, and smoking), intervention (graft, membrane, number of augmented sites/implants), and outcome measurements (follow-up, measurement method, primary/secondary outcome). Any disagreements were discussed with the other two authors (SNP, CHFH).

2.5 | Risk of bias of individual studies

Two authors (NN, HCL) independently evaluated the risk of bias of included studies and any disagreements were discussed with the other two authors (SNP, CHFH). Randomized trials were assessed with the Cochrane risk of bias tool (Higgins & Green, 2011) and non-randomized studies were assessed with the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool

(Sterne, et al., 2016).

2.6 | Summary measures and synthesis of results

The Mean Difference (MD) for continuous variables and the Relative Risk (RR) for binary variables with their corresponding 95% Confidence Intervals (CIs) were chosen a priori for data synthesis of primary or secondary outcomes. As various patient-/, site-/, and graft-specific factors were assumed to influence the true effects of lateral bone augmentation, a random-effect model was a priori chosen in order to incorporate this variability and calculate the mean distribution of these effects. The Paule and Mandel variance estimator was chosen a priori instead of the 'DerSimonian and Laird', due to its improved performance (Veroniki, et al., 2016).

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and calculating the tau^2 (absolute heterogeneity) and the I^2 (relative heterogeneity), respectively; I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance (Higgins & Green, 2011). Heterogeneity was roughly categorized as low, moderate and high according to I^2 values of 25, 50, and 75 per cent, although the heterogeneity's localization on the forest plot was also judged. Additionally, the 95 per cent CIs around tau^2 and I^2 were calculated (Ioannidis, Patsopoulos & Evangelou, 2007) to quantify uncertainty around these estimates. Ninety-five per cent predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which is crucial for the correct interpretation of random-effects meta-analyses (IntHout, Ioannidis, Rovers & Goeman, 2016). All analyses were conducted in Stata SE version 14.2 (StataCorp LP, College Station, Texas, USA) by one author (SNP) with the data made freely available in Zenodo (Naenni, Hyun-Chang Lim, Papageorgiou & Hämmerle, 2018). A two side $P < 0.05$ was considered significant for hypothesis-testing, except for $P < 0.10$ used for tests of between-studies or between-subgroups heterogeneity (Ioannidis, 2008).

2.7 | Risk of bias across studies and additional analyses

Possible sources of heterogeneity were a-priori planned to be sought through mixed-effects subgroup analyses about the combination of different grafts and the use of a membrane. Furthermore, the following meta-analyses (corresponding to individual patient data cumulative meta-regressions) were

performed by meta-analyzing the regression coefficients that originated from re-analysis of available raw data: patient age, patient sex, jaw, mouth region, baseline bone width, healing time and donor site for autologous grafts. Additional analyses for subgroups, meta-regressions and reporting biases were planned, but were not conducted due to lack of available studies (Appendix 2).

Robustness of the results was planned a priori to be checked with sensitivity analyses based on (i) inclusion/exclusion of non-randomized trials, (ii) inclusion only of studies with low risk of bias and (iii) improvement of the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) classification.

The overall quality of clinical recommendations for all meta-analyzed outcomes was rated using the GRADE approach, as very low, low, moderate, or high (Guyatt, Oxman, Schunemann, Tugwell & Knottnerus, 2011) and a Summary of Findings table (Table 3) was constructed using the improved format proposed by Carrasco-Labra et al. (Carrasco-Labra, et al., 2016) and recent guidance on incorporating non-randomized studies (Schunemann, et al., 2018). The minimal clinical important (Norman, Sloan & Wyrwich, 2003) large and very large effects were defined as half, one, and two standard deviations (using the average standard deviation for an outcome across included studies), respectively. Arbitrary cut-offs of 1.5, 2.0, and 5.0 (Schünemann, Brożek, Guyatt & Oxman, 2013) were adopted for RR. The produced forest plots were augmented with contours denoting the magnitude of the observed effects (Papageorgiou, 2014) to visually gauge heterogeneity, clinical relevance and imprecision.

3 | RESULTS

3.1 | Study selection

The literature search yielded a total of 8167 hits, while 7 additional records were identified by hand searching (Fig. 1). After eliminating 1771 duplicates, the titles and abstracts of the remaining papers where scrutinized, leading to the exclusion of another 6332 records. Finally, 71 full texts were checked for eligibility with respect to the inclusion / exclusion criteria. Of these, 41 articles were excluded for various reasons, leaving 30 papers pertaining to 25 unique studies for inclusion in the present systematic review (Appendix 3). All but one included articles reported on feasibility of implant placement after healing times ranging from 3.0 to 8.1 months, whereas four out of these studies followed the inserted implants up to 10 years (Table 1b,c).

3.2 | Study characteristics

The characteristics of the 25 included studies are descriptively analyzed in Table 1a. Sixteen studies (64%) were randomized clinical trials (13 with parallel and 3 with within-patient randomization), while the remaining 9 (36%) were non-randomized comparative studies (5 explicitly prospective and 4 with unclear design). Most studies were performed in a university setting (n=16; 64%), followed by hospitals (n=3; 12%), a private practice (n=1; 4%) and a combination of university and private practice (n=1; 4%). The included studies were conducted in fifteen different countries, encompassing a patient population of 553 individuals (all studies reported on the number of patients) with a mean age of 43.9 years (data from 18 studies reporting on age), of whom 42.2% were male (from 18 studies reporting on sex). The recipient sites of the included studies were as follows: 9 studies solely in the maxilla (6 in the anterior area, 3 in either anterior and posterior areas), 3 studies solely in the posterior mandible, 7 studies investigated in both jaws, whilst 6 studies did not report on the region investigated. After primary lateral augmentation, sites had been left for healing between 3.0 - 8.1 months before re-entry / implant placement (Table 1b). At least 761 implants (15 studies reported on the number of implants) were placed in at least 574 sites (reported in 25 studies). Twenty-three studies reported clinically and/or radiographically measured bone width changes (Table 1a). Implant feasibility was reported in all but in one study (Table 1c), complications in 17 studies (Table 1d), implant survival rate in 4 studies (Table 1b), implant success rate in 3 studies (Table 1b), PROMS in two studies and marginal bone loss in 2 studies (Table 1b). The other outcomes irrelevant to the present review included bone quality, ISQ value, peri-implant health, esthetic index, bone microstructure, bone volume, histologic outcomes, soft-tissue volume.

3.3 | Risk of bias within studies

The risk of bias for the included randomized trials was assessed using the Cochrane Risk of Bias tool and is presented in Fig. 2a and Appendix 4a. None of the included studies had an overall low risk of bias. Only two studies had no high risk of bias for any of the assessed domains (de Freitas, et al., 2016; Eskan, et al., 2014) and were thus judged to have an overall unclear risk of bias. Only three studies presented more than 50% of low risk in all seven domains (Badr, et al., 2010; de Freitas, et al., 2016; Eskan, et al., 2014) and eight studies presented more than 50% of unclear risk (Aarújo, 2016;

Antoun, Sitbon, Martinez & Missika, 2001; Caldwell, Mills, Finlayson & Mealey, 2015; Costa, et al., 2011; Kheur, et al., 2018; Mazzocco, Nart, Cheung & Griffin, 2011; Pourabbas & Nezafati, 2007; Thoma, et al., 2018). The most problematic domains with high risk of bias were "missing or incomplete blinding", "incomplete outcome data" and "other sources of bias". Additionally, none of the identified studies had a pre-defined registered protocol and the risk for "selective outcome reporting" bias was unclear in all publications.

The risk of bias for the included non-randomised studies according to the ROBINS-I tool is presented in Fig. 2b and Appendix 4b. None of the studies presented low level of overall bias (one for moderate bias (Beitlitum, Artzi & Nemcovsky, 2010), five for serious bias (Barbu, et al., 2016; Cordaro, et al., 2002; Maiorana, Beretta, Salina & Santoro, 2005; Shalash, et al., 2013; Urban, et al., 2011) and three for critical bias (Chiapasco, Abati, Romeo & Vogel, 1999; Dasmah, Thor, Ekestubbe, Sennerby & Rasmusson, 2013; Monje, et al., 2014). The domain “bias due to confounding” was a source for critical risk of bias for three studies with overall critical risk of bias (Chiapasco, et al., 1999; de Freitas, et al., 2016; Monje, et al., 2014). The domain “bias due to missing data” was judged as unclear in all studies. The domains “bias due to confounding” and “bias in measurement of outcomes” was judged as serious in more than 50% of the studies.

3.4 | Results of individual studies and synthesis of results

In general, a wide variability regarding materials and techniques investigated as well as parameters reported was observed in the included studies (Table 1a-d). All studies gave to some extent descriptive aggregate data of their results, while 9 studies [four randomized (Aarújo, 2016; Caldwell, et al., 2015; Meijndert, Raghoebar, Schupbach, Meijer & Vissink, 2005; Thoma, et al., 2018) and five non-randomized (Barbu, et al., 2016; Chiapasco, et al., 1999; Maiorana, et al., 2005; Monje, et al., 2014; Urban, et al., 2011)] also provided raw data in tabular form within the published report. Available raw data were re-analyzed with generalized linear regression models and are reported in full in Appendices 5-13.

3.5 | Synthesis of results

Overall, bone width pre-augmentation measured 2.96mm (95% CI: 2.69 to 3.23; I^2: 97%), whilst bone width post-augmentation measured 7.68mm (95% CI: 7.11 to 8.24; I^2: 96%). Due to graft resorption (-

1.33mm (95% CI: -1.78 to -0.88; I^2: 93%), bone width at re-entry resulted in a mean of 6.36 mm (95% CI: 5.73 to 6.99 mm; I^2: 98%). Thus, an overall mean bone width gain of 3.30mm (95% CI: 2.81 to 3.79; I^2: 97%) could be achieved (Table 1e). Data resulting from re-analysis of the seven studies that provided raw data (Aarújo, 2016; Chiapasco, et al., 1999; Cordaro, et al., 2011; Eskan, et al., 2014; Maiorana, et al., 2005; Mordenfeld, Johansson, Albrektsson & Hallman, 2014; Thoma, et al., 2018) resulted in very similar pooled averages (Table 1f).

Only a limited number of factors could finally be analyzed with random-effects meta-analyses: (i) a comparison pertaining to the use of an autologous graft (AUG) versus a xenograft (XEN) mixed with/without AUG (Aarújo, 2016; Barbu, et al., 2016; Cordaro, et al., 2011; Maiorana, et al., 2005; Urban, et al., 2011) (Table 2a, Fig. 3a, b) and (ii) a comparison for lateral bone augmentation with or without the use of a membrane (Antoun, et al., 2001; Chiapasco, et al., 1999) (Table 2b; Fig. 3a, b).

Meta-analysis on the use of XEN (with/without AUG) compared to the use of AUG alone (Table 2a, Fig. 3a) did not find a statistically significant difference in the amount of BW gain (Aarújo, 2016; Barbu, et al., 2016; Cordaro, et al., 2011; Maiorana, et al., 2005; Urban, et al., 2011) (MD: 0.32 mm; 95% CI: -0.19 to 0.83 mm; $p>0.05$). On the other hand, sites augmented with XEN (with/without AUG) showed significantly less absolute graft resorption compared to sites augmented with AUG alone (MD: 1.06 mm; 95% CI: 0.21 to 1.92 mm; $p=0.01$) (Fig. 3b), with moderate heterogeneity across studies (I^2: 63%). This was also reflected by graft resorption compared to the amount of bone graft added to the site, where sites augmented with XEN (with/without AUG) resulted in 11.6% less resorption of the added graft compared to AUG alone (MD: 11.6%; 95% CI: 5.2 to 18.1%; $p<0.001$).

The use of a membrane with lateral augmentation could be assessed in a meta-analysis of two studies (Antoun, et al., 2001; Chiapasco, et al., 1999) (Table 2b). No statistically significant advantage could be observed regarding neither BW gain (MD: -0.33 mm; 95% CI: -2.24 to 1.58 mm; $p>0.05$) nor absolute graft resorption (MD: 0.84 mm; 95% CI: -1.42 to 3.09 mm; $p>0.05$) with the use of a membrane compared to no membrane (Fig. 3a, b).

Furthermore, meta-analysis of the regression coefficients from the raw data of each study listed in Appendices 5-13 was used to assess the effect on the outcome of lateral augmentation of the following patient-/ graft-/ or surgery-related factors: age, sex, jaw, region, baseline BW, healing time and donor site for AUG (Appendix 14a-c). Regarding BW gain, the single predicting factor was baseline BW, where sites with greater pre-augmentation BW tended to have less benefit (pooled

effect: -0.35 mm; 95% CI: -0.63 to -0.07 mm; p=0.01) (Appendix 14a). As far as absolute bone graft resorption is concerned, no significant modifying factor was identified, although there was a trend for maxillary sites to present greater post-augmentation resorption compared to mandibular sites (pooled effect: -0.21 mm; 95% CI: -0.47 to 0.05 mm; p=0.12) (Appendix 14b). Finally, as far as % bone graft resorption of the added graft is concerned, BW at baseline was again inversely associated with BW gain. Increased baseline BW of the site was associated with increased % resorption (pooled effect: -4.7%; 95% CI: -9.9 to 0.5%; p=0.07) (Appendix 14c). Additionally, patient age had a significant influence, with older patients presenting higher % resorption (pooled effect: -0.4% per year; -0.6% to -0.1% per year; p=0.01).

3.6 | Additional analyses and Risk of bias across studies

A large number of subgroup and meta-regression analyses had been initially planned, but could ultimately not be conducted (Appendix 2). The only subgroup analysis that could be performed pertained to the meta-analysis of BW gain with the use of an autologous graft (AUG) versus a xenograft (XEN) mixed with/without AUG (Table 2c; 5 studies). No statistically significant differences could be found when comparing (i) the use of XEN versus AUG and the use of XEN-AUG versus AUG or (ii) the use of a membrane or not.

A sensitivity analysis was conducted by excluding non-randomized studies and including only randomized studies in the analysis (Appendix 15). The comparisons of lateral bone augmentation with AUG versus a xenograft XEN mixed with/without AUG were relative robust to the inclusion of only randomized trials, as still no statistically significant differences were found. On the other side, sensitivity analysis on membrane use gave slightly different results. For one, now the BW gain when using a membrane was greater compared to no membrane use. Nevertheless, this difference did not reach statistical significance. This was in contrast to the original analysis that showed the opposite (MDs of -0.33 mm for the original and 0.80 mm for the sensitivity analysis). Additionally, membrane use was associated with a significantly lower amount of post-augmentation graft resorption compared to no use of membrane (MD: 2.0 mm; 95% CI: 1.3 to 2.8 mm; p<0.001), which was contrary to the original analysis from randomized and non-randomized studies.

The quality of evidence from all meta-analyses was finally gauged with the GRADE approach using the original analyses, except for the case of bone graft resorption with/without membrane,

where the sensitivity analysis was used (Table 3). All meta-analyses were judged to provide very low quality of evidence due to the inclusion of non-randomized studies, the high risk-of-bias of both randomized and non-randomized included studies, and imprecision due to limited sample sizes. The only exception was the sensitivity analysis assessing bone graft resorption with or without the use of membrane, where moderate quality of evidence favored membrane use—with the only limitation being the high risk-of.bias in the included randomized trial.

4 | DISCUSSION

4.1 | Summary of evidence

The literature search yielded a total of 25 studies, of which 16 were randomized and 9 were non-randomized comparative studies including at least 553 patients (mean age 43.9 years/ 42.2% male) and at least 761 dental implants that had been placed after a healing-time of 3.0-8.1 months following primary horizontal augmentation.

The results of the current systematic showed that: i) feasibility of implant placement was achieved in the majority of the studies, although sometimes requiring additional GBR at the time of implant placement; ii) bone width (BW) gain was significantly influenced by BW at baseline; iii) age revealed a significant association with bone graft resorption favoring younger patients; iv) groups using xenograft showed significantly less graft resorption compared to autologous graft alone, but did not lead to a statistically significant difference in BW gain and v) the use of a membrane did not result in superior BW gain compared to augmentation without a membrane.

Bone width gain

This systematic review revealed that horizontal ridge augmentation prior to implant placement was successful in terms of BW gain. Nevertheless, some studies reported on the need for additional bone augmentation at the time of implant placement (Badr, et al., 2010; Beitlitum, et al., 2010; Chiapasco, et al., 1999; Kheur, et al., 2018; Meijndert, et al., 2005) or the need for the placement of a narrower implant diameter than planned (Eskan, et al., 2014). In case of insufficient ridge width after bone augmentation, the placement of a smaller diameter implant or a simultaneous bone augmentation might be considered. Interestingly, BW at baseline (prior to augmentation) was significantly inversely correlated with the obtained BW gain (see supplement 14a), which indicates that the thinner the

baseline BW was, the more BW gain could be achieved. This observation might be due to two potential reasons: i) the resorptive pattern may tend to follow the natural anatomy of the original ridge and/or ii) the more ridge width is present prior to augmentation, the less bone graft material is applied.

One study demonstrated that bone augmentation within the bony envelope is highly predictable compared to that outside of the bony envelope (Tinti & Parma-Benfenati, 2003). Thus, when overbuilding is performed out of the ridge anatomy, one should consider the possibility of future resorption. However, there has been no long-term study to investigate this issue.

Moreover, when performing a ridge augmentation procedure, it is important to know what amount of graft material is required depending on the prosthetic planning (Chiapasco & Casentini, 2018). Within the present review, most of the authors seemed to aim at placing regular diameter implants ranging from 3.5 to 4.1 mm (Table 1c), which may indicate that 6-7 mm of BW could be considered sufficient for implant placement. If, for example 4 mm of residual BW is present (reported as baseline BW in some studies), there might be no reason to apply a great amount of bone graft material. As a consequence, the anticipated final BW has to be taken into account when performing ridge augmentation procedures, without disregarding expected resorptive processes.

Implant feasibility

Implant feasibility reflects the most important parameter in assessing the success of primary bone augmentation. Ideally, implant planning - such as prosthetically ideal positioning, implant diameter and length - should be determined preceding primary bone augmentation (Chiapasco & Casentini, 2018). Based on the literature search, only one study reported specifically on pre-augmentation implant planning (Eskan, et al., 2014)(Table 1c). In that study, the predictability of planned implant placement reached 100% in one group and 93% in the other group. Eleven studies reported on implant diameter, although without giving further information regarding the placement thereafter. The rest of the included studies did not provide information regarding implant diameter. Authors used terms such as 'proper implant placement' and 'suitable sized implant'. The above-described main findings were not reported in a way that allowed for proper statistical analysis, but are reported in a descriptive manner within this investigation. Hence, the original primary aim of this systematic review had to be changed to BW gain and graft resorption.

Graft resorption

Meta-analysis of the regression coefficients indicated a relationship between % graft resorption and patient age (P<0.01; Appendix 14c). Age has been controversially discussed as a factor influencing implant success (Bartold, Ivanovski & Darby, 2016; Ikebe, Wada, Kagawa & Maeda, 2009). Presumably older patients may exhibit poorer local bone condition, require longer healing periods and display more systematic diseases related to healing potential in general. Based on the meta-analysis, this review revealed that every additional year of age at the time of primary augmentation led to 0.05 mm (95% CI: -0.03 to 0.12 mm; p=0.20) more absolute resorption of the augmented bone (Appendix 14b). For example, a 60-year old patient would experience 1 mm more graft resorption post-augmentation compared to a 40-year old patient. This age-dependent resorptive pattern could perhaps become more clinically relevant due to current aged or ultra-aged society (Muramatsu & Akiyama, 2011).

Regarding the outcomes for the recipient jaw, results were potentially in favor of the mandible. Thus, absolute graft resorption was more pronounced in the maxilla (difference: -0.21 mm; 95% CI: -0.47 to 0.05 mm), even though this was not statistically significant (p=0.12), probably due to low power (Appendix 14b). Possible cause-effectors might be the level of surgical difficulty especially in the posterior maxilla, extensive overbuilding in the anterior maxilla or uneven pressure of soft tissue after closure of the flap. One might initially expect that extensively resorbed mostly cortical mandibles might yield unfavorable augmentation results due to reduced vascularization. However, radiographic evidence indicates that the blood vessels remain within the central canals of resorbed osteons and even the densest-appearing cortex is actually porous (Atwood, 1962).

Presence of xenograft

The presence of a xenograft lead to decreased graft resorption compared to autologous grafts alone. These results seem somehow contradictory, originating from 5 studies for BW gain (showing no significance) compared to 3 studies having been analyzed for graft resorption. Three authors (Barbu, et al., 2016; Cordaro, et al., 2011; Maiorana, et al., 2005) have used the autologous block with particulated xenogenic graft material ("added at the periphery", "in order to fill gaps and defects" and "over the graft"), whereas one study had used particulated autologous graft mixed with particulated xenograft in a 1:1 ratio (Urban, et al., 2011) and one had used a xenograft block alone (Aarújo, 2016).

Sites augmented with xenogeneic graft materials with or without autologous bone particles XEN (with/without AUG) revealed 11.6% less resorption compared to sites augmented with autologous grafts alone AUG (MD: 11.6%; 95% CI: 5.2 to 18.1%; p<0.001) (Table 2a). These results support the assumption that the presence of a xenograft prevents from bone resorption. This might be due to its slow resorption rate and thus long standing-time (Schlegel & Donath, 1998; Skoglund, Hising & Young, 1997).

Use of membrane

Although the use of a membrane is supposed to prevent soft tissue ingrowth (Dahlin, Linde, Gottlow & Nyman, 1988; Kostopoulos & Karring, 1994), augmentation without membrane coverage did not demonstrate significant differences in terms of BW gain and graft resorption within this study. The two studies investigating the use of a non-resorbable membrane (Antoun, et al., 2001; Chiapasco, et al., 1999) applied an autologous block bone graft without a membrane and compared this treatment with either a GBR procedure (particulated autologous bone and membrane) or an autologous block graft with membrane coverage. These results were to some extent unexpected. A wide body of evidence exists on the procedure of bone augmentation and the use of membranes in order to maintain space, prevent soft tissue ingrowth and to help stabilize the augmented area. This may have played a minor role in the two before-mentioned studies, as bone block grafts were used. The cortical layer of the bone block might be sufficient to prevent soft tissue ingrowth and resist to resorption. Additionally, the fixating screws may have given the bone block graft sufficient stability. Evidence regarding no need to use a membrane shall be perceived whilst keeping this in mind.

Bone width measurements

Bone width gain was measured in the included studies either clinically and/or radiographically, while only one study transparently provided results of both clinical and radiographic measurements (de Freitas et al., 2013). Although small discrepancies were found between overall clinical and radiographic gain (pooled gains of 3.45 ± 1.18 mm versus 2.90 ± 0.83 mm, respectively), these were not statistically significant. However, both the bone gain magnitude and the variation of the measurements (seen through the standard deviation) was consistently lower radiographically than clinically, which might indicate greater measurement accuracy for the radiographic method.

Additionally, radiographic evaluation of bone width enables a more comprehensive assessment of the alveolar width at different heights. For example, the same study (de Freitas et al., 2013) reported considerable differences in bone width gain according to height below the alveolar crest (pooled gains: 1.00 ± 0.94 mm 2 mm below crest, 2.90 ± 0.83 mm 6 mm below crest, and 1.75 ± 0.98 mm 10 mm below crest). This indicates a possibly uneven pattern of post-augmentation resorption and final bone width gain that might have a direct clinical relevance and is therefore an interesting aspect for future research.

4.2 | Strengths and limitations

The strengths of this systematic review consist of the registration of its *a priori* protocol in PROSPERO (Sideri, Papageorgiou & Eliades, 2018), its exhaustive literature search, its improved analytical methods (Veroniki, et al., 2016), the use of the GRADE approach (Guyatt, et al., 2011) to assess the quality of the meta-evidence, and the transparent provision of the study's data (Naenni, et al., 2018). Additionally, only randomized and prospective non-randomized comparative studies were included in this systematic review, which are less biased than retrospective non-randomized studies.

However, certain limitations do exist mainly due to the vast methodological and clinical heterogeneity of the identified studies. First, the initially planned primary outcome of the review pertaining to implant feasibility was discarded as the primary outcome, since no study but one transparently reported on deviations from implant size that was originally planned and implant size that was eventually inserted. Results on feasibility are reported as secondary outcomes and in a descriptive manner. Second, data on post-augmentation BW gain were measured in the identified studies (Beitlitum, et al., 2010; de Freitas, et al., 2013; de Freitas, et al., 2016; Mazzocco, et al., 2011) either clinically or radiographically, although hints exist that the measurement method might have a direct influence on the observed BW. Third, a few secondary outcomes could not be statistically analyzed due to study characteristics and thus are only descriptively reported within this review. Peri-implant health would have been an outcome of most interest, especially in implants placed after primary lateral augmentation. Unfortunately, only two of the included studies investigated this parameter (Cordaro, et al., 2011; Meijndert, et al., 2017). Furthermore, methodological issues existed for all included studies, as has been often reported for clinical trials in implant dentistry (Papageorgiou, Kloukos, Petridis & Pandis, 2015), and these might have influenced the review's results. This is

especially the case for included non-randomized studies that were not clearly retrospective and not clearly prospective—even though a sensitivity analysis of only randomized studies indicated robustness of the results. Furthermore, the identified studies reported predominantly on small sample sizes and this might have introduced small-study effects (Cappelleri, et al., 1996). Also, analysis was performed on augmentation site level, which ignores clustering effects and might lead to information loss, except for studies where full data were openly available and were analyzed appropriately (Appendix 5-13). The limited number of included studies and their suboptimal reporting did not enable robust assessments of heterogeneity, as well as the conduct of several analyses for subgroup, and small-study effects that were planned. Finally, no formal assessment of reporting biases was possible due to the small number of included studies and the lack of published trial protocols, even though our comprehensive and unrestricted literature search might partially safeguard against reporting bias.

5 | CONCLUSIONS

Based on the results from the included randomized and prospective non-randomized trials, primary lateral bone augmentation leads to sufficient bone width and allows for subsequent implant placement in most cases. In general, initially smaller bone dimension is associated with larger bone width gain, which indicates that a severe lateral bone deficiency can be effectively augmented applying primary lateral bone augmentation. Patients' age and recipient site (maxilla or mandible) seems to influence graft resorption. The addition of a xenograft can be helpful for reducing graft resorption. However, the quality of clinical recommendation that can be drawn at the present time ranges from moderate to very low, due to the limited number of existing studies and their methodological shortcomings.

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AUTHORS' CONTRIBUTIONS

Nadja Naenni: Protocol development, Inclusion/Exclusion of Studies, Drafting of article, Critical revision and Approval of article

Hyun-Chang Lim: Protocol development, Inclusion/Exclusion of Studies, Drafting of article

Spyridon N. Papageorgiou: Protocol development, Data collection, Analysis and Interpretation, Critical

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Figure legends

Figure 1. Flow diagram for the identification and selection of eligible studies for this systematic review.

* descriptive data were missing to include the studies in the analyses.

Figure 2a. Risk of bias summary of included randomized trials with the Cochrane risk of bias tool.

2b. Risk of bias summary of included non-randomized trials with the ROBINS-I tool.

Figure 3a. Contour-enhanced forest plot on the amount of bone width gained from lateral augmentation. AUG, autologous graft; CI, confidence interval; MD, mean difference; WO/W, with/without; XEN, xenograft.

3b. Contour-enhanced forest plot on the amount of graft resorption during lateral augmentation. AUG, autologous graft; CI, confidence interval; MD, mean difference; WO/W, with/without; XEN, xenograft.

TABLE LEGENDS

Table 1a. Characteristics of included studies.

* countries are given with their ISO Alpha-3 codes

† age is given in years as either mean (one value) or if mean not reported as range (two values in parenthesis)

§ excluding two patients being in both groups from the age-counting

ALG: allogenic graft; ALP: alloplastic grafts; ANT: anterior; AUG: autologous graft; G1,G2: group 1, group 2; hosp: hospital; Max: maxilla; MC: Multi-center; MEM: membrane; Mnd: mandible; NR: not reported; NRES: non-resorbable; Pats: patient; pNRS: prospective non-randomized study; POS: posterior; pract: private practice; pRCT: parallel randomized clinical trial; PRF: platelet-rich fibrin; PRP: platelet-rich plasma; RE: ridge expansion; RES: resorbable; RS: ridge-splitting; SD: systemic disease; Univ: university clinic; uNRS: non-randomized study with unclear design; wpRCT: within-person randomized clinical trial; XEN: xenograft.

Table 1b. Outcomes assessed by included studies.

‡ follow-up after augmentation is given in months as either mean (one value) or if mean not reported as range

§ two patients are in both groups

BW: bone width; BQ: bone quality; CLIN: clinical; CoI: Conflict of Interest; Compl: Complication; FU: follow-up; Imp: implantation; ImpIns: implantation insertion; Imp success: Implant success; Imp survival: Implant survival; NR: not reported; RAD: radiography.

Table 1c. Implant information by included studies.

placed: Number of implants placed; planned: Number of implants planned; Implant diameter: Implant diameter in mm; additional GBR at the time of implant placement: Guided bone regeneration (GBR) performed at the time of implant placement; Comment: Additional information given by the authors.

Table 2a. Random-effects meta-analyses on use of xenograft for lateral augmentation (experimental) compared to use of autologous graft (reference).

BW: bone width; CI: confidence interval; MD: mean difference; NC: non calculable.

Table 2b. Random-effects meta-analyses on membrane use during lateral augmentation (experimental) compared to no membrane use (reference).

BW: bone width; CI: confidence interval; MD: mean difference; NC: non calculable.

Table 2c. Subgroup analysis for the meta-analysis on use of xenograft for lateral augmentation (experimental) compared to use of autologous graft (reference) and with the outcome of bone width gain.

AUG: autologous graft; CI: confidence interval; MD: mean difference; XEN: xenograft.

Table 3. Summary of findings table according to the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Factors associated with outcome of lateral bone augmentation.

Population & intervention: partially/fully edentulous adult patients with resorbed alveolar bone receiving lateral bone augmentation prior to dental implant treatment.

Settings: university clinics and private practice.

a The basis for the risk in the control group (e.g., the median control group risk across studies) is provided in footnotes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

b Reponse in the control group is based on pooled Paule-Mandel meta-analyzed effect in the control group.

c GRADE for both randomized and non-randomized studies starts from “high”.

d Downgraded initially to ‘low’ due to the inclusion of non-randomized studies; further downgraded to very low for lack of blinding serious limitations (high risk of bias).

e Imprecision also identified due to the limited sample size finally included; however GRADE is already at very low.

f The single identified trial was in high risk of bias due to incomplete reporting of data; downgraded by one.

CI: confidence interval; CTR: control category; EXP: experimental category; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: mean difference.

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